REMARKS

Claims 1-23 were filed in the original case. Claims 1-23 were cancelled in a previous amendment. Claims 24-61 were added in a previous amendment. Therefore, Claims 24-61 are currently pending.

In the Office Action dated August 26, 2003, the Examiner has made a number of rejections. The currently pending rejections are:

1) Claims 24-38, 40, 43, 44, 49-26, and 58 are rejected under 35 U.S.C. 102(b); and
2) Claims 41, 45-48, and 59 are rejected under 35 U.S.C. 103(a); and
3) Claims 42 and 60 are rejected under 35 U.S.C. 103(a); and
4) Claims 39, 57 and 61 are rejected 35 U.S.C. 103(a).

The Applicants believe that the pending claims are not taught by the prior art and are not obvious. Therefore, Claims 24-61 should be passed into allowance.

REJECTIONS

I. THE AUGUST 26, 2003 OFFICE ACTION IS IMPERMISSIBLY FINAL

The Examiner argues (Office Action 8/26/2003): "Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a)." No support is given for this statement—i.e., the Examiner has not pointed to which amendment or amendments necessitated the new grounds of rejection or why such amendment necessitated the new grounds of rejection.

To the contrary, the Applicant's amendment made in the "Amendment and Response to Office Action Dated February 4, 2003" does **NOT** present new grounds for rejection. Independent Claim 1 as originally filed reads:

1. A method for reducing the activity of an RNase, comprising:

a) providing

i) a preparation comprising at least one RNA polymer;

ii) a sample containing an RNase; and

b) mixing said preparation with said sample under conditions such that the activity of said RNA binding enzyme is diminished relative to the activity of said RNase in the absence of said RNA polymer.

Independent Claim 24 and independent Claim 44 as amended in the Response to Office Action dated February 4, 2003 read:

24. A method for reducing the activity of an RNase, comprising:

a) providing

i) a preparation comprising at least one RNA heteropolymer;

ii) a sample containing an RNase; and

b) mixing said preparation with said sample under conditions such that the activity of said RNase enzyme is diminished relative to the activity of said RNase in the absence of said RNA heteropolymer.

44. A method for reducing the activity of an RNase, comprising:

a) providing

i) a preparation comprising at least one isolated, unmodified RNA homopolymer;

ii) a sample containing an RNase; and

b) mixing said preparation with said sample under conditions such that the activity of said RNase enzyme is diminished relative to the activity of said RNase in the absence of said RNA homopolymer.

Applicants note that the present claims have split the previous claims (which claimed heteropolymers and homopolymers) into a first set of claims (24-43) that comprise heteropolymers, and a second set of claims (44-61) that comprise homopolymers. Hence, "polymer" in independent Claim 1 as originally filed has been split to "heteropolymer" in independent Claim 24, and "homopolymer" in independent

Claim 44. No other amendments have been made to the wording, language or meaning of the amended Claims. Therefore, the Examiner is in error in determining that the amendment of the Response to Office Action dated February 4, 2003 necessitates new grounds of rejection as asserted by the Examiner in the Office Action of August 26, 2003. Applicants have not changed the scope of the claims in a manner relevant to the rejections. The previous rejections were withdrawn based on Applicants' arguments, not the amendments. There is no new issue raised by the amendments.

Indeed the Office Action of August 26, 2003 proffers only a single additional reference (Raines et al.). Raines could have been cited in the original rejection. Applicants' amendments did not necessitate the new grounds of rejection—they were necessitated by the failure of the originally cited prior art to teach or suggest the claimed invention. Accordingly, Applicant requests that the determination of finality for the Office Action of August 26, 2003 be withdrawn.

II. THE CLAIMS ARE NOT ANTICIPATED

The Examiner has rejected the claims 24-38, 40, 43, 44, 49-56, and 58 as allegedly being anticipated by Raines et al. (U.S, Patent 5,389,537). The Federal Circuit has stated the relevant analysis for anticipation as follows:

> "A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference."[1]

The prior art cited by the Examiner consists of Raines et al. (U.S, Patent 5,389,537). The Examiner argues that "Raines et al teach a method for reducing the activity of an RNAse (Abstract), comprising: a) providing I) a preparation comprising at least one RNA homopolymer and heteropolymer (Column 4, lines 42-66, Table 1 and Column 8, lines 34-47." (Office Action, August 26, 2003, page 2)

[1] *Verdegaal Bros. V. Union Oil of California*, 2 USPQ2d 1051, 1053 (Fed.Cir. 1987)

1. Raines et al. does not anticipate the Claims of the Present Invention

Contary to the Examiner's argument, Raines et al. does not teach a method for reducing the activity of an RNAse. Rather, it teaches a mutant RNAse protein that cleaves after a C, U or A residue, in comparison with wild-type RNAse that "cannot cleave efficiently after an A." (Raines et al., Abstract) Raines makes no mention of wild-type or mutant RNAse inhibition with an RNA homoploymer, heteropolymer or polymer of any kind. The present claims are directed to a method whereby an RNA polymer reduces the activity of an RNase relative to the activity of the same RNase in the absence of the polymer. Raines only compares the behavior of the mutant ribonuclease to wild-type ribonuclease, not the individual enzyme activities to themselves in the presence and absence of polymer. For example, Raines does not teach or suggest that an RNA polymer, when exposed to an RNase, reduces the activity of the RNase in digesting RNA in a sample. This is not the purpose of the Raines work and was not addressed in Raines. For example, nothing in Raines teaches or suggests that one can or should use RNA polymers (heteropolymers or homopolymers) to prevent RNases contained in a sample from digesting desired RNA molecules in the sample—one of the valuable uses of one embodiment of the presently claimed invention (e.g., use of polymers in RT-PCR reactions to prevent RNases from degrading the desired RNA molecules to be amplified in the PCR).

The Examiner mischaracterizes Raines Table 1 and Column 8, lines 34-47 as evidence that Raines anticipates the present invention. To the contrary, Table 1 and Column 8, lines 34-47 describe only "the efficiency with which T45G and T45A RNase A cleave poly(A), the steady-state kinetic parameters for the cleavage of the synthetic substrate UpA and the homopolymers poly(A) , poly(C), and poly (U)" compared to each other and to wild-type RNase A. In Table 1, and Column 8, lines 34-4, the RNA homopolymers poly(A), poly(C) and poly(U) are evaluated as substrates for mutant and wild-type RNAse activity (not inhibition) independently of one another. The homopolymers are not evaluated in the presence of one another at different time points as would be needed in these particular experiments to detect and measure inhibition of the enzyme. Therefore, Table 1 and Column 8, lines 34-47 of Raines teach comparative activity (not inhibition) of two mutant and one wild-type RNAse A against poly(A),

poly(C) and poly(U) in isolation from one another, but do not teach inhibition of RNAse A whatsoever.

2. Raines et al. does not teach the homopolymers and heteropolymers of the present Dependent Claims

The Examiner has rejected many of Applicants' dependent claims that recite specific homopolymers and heteropolymers as being anticipated by Raines. However, Raines does not mention many of these homopolymers and heteropolymers in any context (for the reasons discussed above, even those that are mentioned do not anticipate the present claims). For example, Raines does not mention the following heteropolymers of the presently claimed invention: polyA;polyU (Claim 29), polyC:polyG (Claim 30), poly(GU) (Claim 31), poly(CU) (Claim 32), poly(GI) (Claim 33), or poly(CI). Raines further does not teach double-stranded heteropolymers or single-stranded heteropolymers. Raines does not teach even a single heteropolymer for any purpose. Synthetic UpA reported in Table 1 and Column 8, lines 34-47 is uridylyl(3',5')adenosine, and is not a polymer. As well, Raines does not mention the homopolymers poly(I) (Claim 49) and poly(G) (Claim 51) for any purpose, or any method. In the Office Action dated August 26, 2003 the Examiner has failed to address the absence of these homopolymers and heteropolymers from the cited Raines reference.

Applicants respectfully submit that the Raines reference does not teach each and every element of the Claims as required by the CAFC, and requests that the rejection under 35 USC §102b be withdrawn.

II. THE CLAIMS ARE NOT OBVIOUS

In rejecting claims under 35 U.S.C. 103(a) the Examiner has made a number of combinations of Raines et al. with Berger et al, Chatterjee et al. and Akitaya et al. None of these references alone, or in combination, teach or suggest the presently claimed invention. As discussed above, Raines fails to teach or suggest all of the elements of the independent claims. Berger, Chatterjee, and Akitaya do not remedy this deficiency (nor does the Examiner argue that these reference address the independent claims—they are

simply cited to address specific elements in certain dependent claims). Because the independent claims are not taught by the prior art, the dependent claims are, by definition, novel and non-obvious, as they incorporate all of the elements of the independent claims.

A. Claims 41, 45-48 and 59 are not obvious over Raines et al. in view of Berger et al.

The Examiner has rejected claims 41, 45-48 and 59 as allegedly being obvious in view of Raines et al. in view of Berger et al. The Examiner argues "Raines et al teach the method of claims 24-38, 40, 43, 44, 49-56, and 58 as described above." (Office Action, August 26, 2003, page 4). To the contrary, as detailed in the present response to the Examiner's 35 U.S.C. 102(b) rejection above, Raines et al does not, and cannot, teach the method of claims 24-38, 40, 43, 44, 49-56, and 58.

The Examiner argues "It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute and combine a method for reducing the activity of an RNAse, wherein the activity of the RNAse is diminished at least 25-90% relative to the activity of the RNAse in the absence of the RNA polymer of Berger et al in the method of Raines et al. since Berger et al. state , "The use of this inhibitor (i.e. vanadyl ribonucleoside complex or VRC) should therefore be considered for all tissues in which ribonucleases impede isolation of intact RNA (Abstract, last sentence) ". An ordinary practitioner would have been motivated to substitute and combine a method for reducing the activity of an RNAse, wherein the activity of the RNAse is diminished at least 25-90% relative to the activity of the RNAse in the absence of the RNA polymer of Berger et al in the method of Raines et al, in order to achieve the express advantages noted by Berger et al. of an inhibitor which should be considered for all tissues in which ribonucleases impede isolation of intact RNA." (Office Action, August 26, 2003, pages 4-5).

The Applicants assert that the Examiner has not met the burden of establishing a *prima facie* case of obviousness. A *prima facie* case of obviousness requires the Examiner to cite to references that (a) disclose all the elements of the claimed invention, (b) suggest or motivate one of ordinary skill in the art to combine or modify those

elements to yield the claimed combination, and (c) provide a reasonable expectation of success should the combination cited by the Examiner be carried out.[2] Failure to establish any one of these three requirements precludes a finding of a *prima facie* case of obviousness and, without more, entitles Applicant to allowance of the claims at issue. At a minimum, the Examiner fails to establish a *prima facie* obviousness 1) because the cited references fail to disclose all elements of the claimed invention, 2) because there is no teaching, suggestion or motivation to make the Examiner's selections and combinations of the cited references. The Applicants assert that the Examiner has failed to establish the requirements for a *prima facie* case of obviousness, thus entitling Applicants to withdrawal of this rejection.

1. The Examiner's cited references fail to disclose all elements of the claimed invention

As described above RNAse inhibitors taught by Raines et al., and Berger et al. (i.e. VRC) do not teach or suggest the use of the RNAse inhibitory polymers of the presently claimed invention. Berger et al. only describes the use of vanadyl complexed ribonucleoside 5'-monophosphates, not RNA homopolymers or heteropolymers. For example, in reference to Figure 1, Berger et al. states "As illustrated in figure 1, most potential nuclease inhibitors were incapable of preventing the degradation of RNA despite their ability to retard nuclease action. Only the equimolar mixture of the four ribonucleoside-vanadyl complexes at 10mM protected the exogenous hnRNA substrate." Thus, Berger et al. does not teach the presently claimed invention. As described above, Raines et al does not teach RNA homopolymers or heteropolymers capable of inhibiting RNAse. Thus, even in combination, Berger et al. and Raines et al. are unable to remedy the defects of one another in failing to teach all elements of the presently claimed invention.

[2] See, e.g., *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); and *In re Dow Chemical Co.*, F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

2. The Examiner's cited references fail to provide a motivation to combine the recited elements

An essential requirement for a *prima facie* case of obviousness is whether a person skilled in the art would be motivated to modify the reference to arrive at the claimed invention.[3] The requirement that the Examiner make a showing of a suggestion, teaching or motivation to combine the prior art references is an essential evidentiary component of an obviousness holding. The factual inquiry whether to combine references "must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with."[4] The law requires that evidence of a suggestion, teaching, or motivation to combine prior art references "must be clear and particular".[5] "Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence."[6]

To the contrary, the Examiner's statements regarding the ordinary artisan's motivation to select and combine references are conclusory and unsupported. The Examiner has provided no support in the form of prior art reference, affidavit, declaration, or concrete evidence other than in the form of an argument, teaching that the artisan of ordinary skill would have been motivated to select and combine Berger et al. with Raines et al. This is because the only source guiding the Examiner to pair Raines et al. with Berger et al. as cited in the August 26, 2003 Office Action is the present invention, that is, through the hindsight of one in possession of the present disclosure. Indeed, Raines et al. explicitly teaches an artisan of ordinary skill away from making the combination in stating: "Wild type enzyme was not distracted by pre-incubation with either poly(A) or poly(C), since it is not processive." (Raines et al., Column 10, lines 44-47).

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[3] *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992)

[4] *In re Sang Su Lee* 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002). See also, *Brown & Williamson Tobacco corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential evidentiary component of an obviousness holding'") (quoting *C.R. Bar, Inc. v. M3 Sys. Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.")

5 *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999), *citing C.R. Bard*, 157 F.3d 1340 at 1352, 48 USPQ2d at 1232.

[6] *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999), citing *McElmurry v. Arkansas Power & Light Co.*, 995 F.2d 1576, 1578, 27 USPQ2d 1129,1131 (Fed. Cir. 1993).

B. Claims 42 and 60 are not obvious over Raines et al. in view of Chatterjee et al.

The Examiner has rejected claims 42 and 60 as allegedly being obvious in view of Raines et al. in view of Chatterjee et al. The Examiner argues "Raines et al teach the method of claims 24-38, 40, 43, 44, 49-56, and 58 as described above." (Office Action, August 26, 2003, page 4). To the contrary, as detailed in the present response to the Examiner's 35 U.S.C. 102(b) rejection above, Raines et al does not, and cannot, teach the method of claims 24-38, 40, 43, 44, 49-56, and 58.

The Examiner argues "It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method, wherein RNAse comprises RNAse A, B or angiogenin of Chatterjee et al in the method of Raines et al. since Chatterjee et al. state, "RI is useful in a variety of molecular biology applications where RNAse contamination is a potential problem (Column 1, lines 39-41)." An ordinary practitoner would have been motivated to substitute and combine the method, wherein RNAse comprises RNAse A, B or angiogenin of Chatterjee et al in the method of Raines et al. in order to achieve the express advantages noted by Chatterjee et al. of RI which is useful in a variety of molecular biology applications where RNAse contamination is a potential problem." (Office Action, August 26, 2003, page 5-6).

1. The Examiner's cited references fail to disclose all elements of the claimed invention

Chatterjee et al. teaches the cloning of genes encoding rat and pig liver ribonuclease inhibitor protein, and its expression in a cellular host. (Chatterjee et al., Abstract). Chatterjee does not teach RNA homopolymers and heteropolymers able to inhibit the activity of RNAse A, B or angiogenin. As described above, Raines et al. does not teach RNA homopolymers or heteropolymers capable of inhibiting RNAse. Thus, even in combination, Chatterjee et al. and Raines et al. are unable to remedy the defects of one another in failing to teach all elements of the presently claimed invention.

2. The Examiner's cited references fail to provide a motivation to combine the recited elements

The Examiner's statements regarding the ordinary artisan's motivation to select and combine references are conclusory and unsupported. The Examiner has provided no support in the form of prior art reference, affidavit, declaration, or concrete evidence other than in the form of an argument, teaching that the artisan of ordinary skill would have been motivated to select and combine Chatterjeeet al. with Raines et al. This is because the only source guiding the Examiner to pair Raines et al. with Chatterjee et al. as cited in the August 26, 2003 Office Action is the present invention, that is, through the hindsight of one in possession of the present disclosure. Indeed, Raines et al. explicitly teaches an artisan of ordinary skill away from making any such combination in stating: "Wild type enzyme was not distracted by pre-incubation with either poly(A) or poly(C), since it is not processive." (Raines et al., Column 10, lines 44-47)

C. Claims 39, 57 and 61 are not obvious over Raines et al. in view of Akitaya et al.

The Examiner has rejected claims 39, 57 and 61 as allegedly being obvious in view of Raines et al. in view of Akitaya et al. The Examiner argues "Raines et al teach the method of claims 24-38, 40, 43, 44, 49-56, and 58 as described above." (Office Action, August 26, 2003, page 4). To the contrary, as detailed in the present response to the Examiner's 35 U.S.C. 102(b) rejection above, Raines et al does not, and cannot, teach the method of claims 24-38, 40, 43, 44, 49-56, and 58.

The Examiner argues "It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method, wherein the ribonuclease inhibitor is RNASIN of Akitaya et al in the method of Raines et al. since Akitaya et al. state, "mRNA in the preparations of lanes 1 (containing RNASIN) and 2 did not experience substantial mRNA degradation (Columns 9, lines 45-46)". An ordinary practitioner would have been motivated to substitute and combine the method, wherein the ribonuclease inhibitor is RNASIN of Akitaya et al in the method of Raines et al. in order to achieve the express advantages, as noted by Akitaya et al of RNASIN which prevents substantial mRNA degradation." (Office Action August 26, 2003, page 6).

1. **The Examiner's cited references fail to disclose all elements of the claimed invention**

Akitaya et al. teaches a method for detecting and quantifying mRNA in a sample (Akitaya et al., Abstract). Akitaya does not teach RNA homopolymers and heteropolymers able to inhibit the activity of RNAse. As described above, Raines et al. does not teach RNA homopolymers or heteropolymers capable of inhibiting RNAse. Thus Akitaya et al. plus Raines et al. does not teach RNASIN, or any other ribonuclease inhibitor, in combination with an RNA homopolymer or heteropolymer and a sample containing an RNAse such that the activity of the RNAse enzyme is diminished relative to the activity of the RNAse in the absence of the RNA homopolymer or heteropolymer. Hence, even in combination, Akitaya et al. and Raines et al. are unable to remedy the defects of one another in failing to teach all elements of the presently claimed invention.

2. **The Examiner's cited references fail to provide a motivation to combine the recited elements**

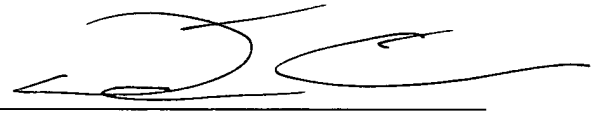
The Examiner's statements regarding the ordinary artisan's motivation to select and combine references are conclusory and unsupported. The Examiner has provided no support in the form of prior art reference, affidavit, declaration, or concrete evidence other than in the form of an argument, teaching that the artisan of ordinary skill would have been motivated to select and combine Akitaya et al. with Raines et al. This is because the only source guiding the Examiner to pair Raines et al. with Akitaya et al. as cited in the August 26, 2003 Office Action is the present invention, that is, through the hindsight of one in possession of the present disclosure. Indeed, Raines et al. explicitly teaches an artisan of ordinary skill away from making any such combination in stating: "Wild type enzyme was not distracted by pre-incubation with either poly(A) or poly(C), since it is not processive." (Raines et al., Column 10, lines 44-47)

In view of the above, Applicant respectfully request that the obviousness rejection be withdrawn.

CONCLUSION

All grounds of rejection of the Office Action of August 26, 2003 have been addressed and reconsideration of the application is respectfully requested. It is respectfully submitted that Applicant's claims as amended should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: 10/27/03



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